TRANSMITTAL OF APPEAL BRIEF (Small Entity)

Docket No.
MSU 4.1-406

In Re Application Of: **Alberto L. Mendoza**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/082,112	May 20, 1998	Brian J. Gangle	21036	1645	2322

Invention: **METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER ANIMALS**

COMMISSIONER FOR PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed on:

September 11, 2006

☐ ☒ Applicant claims small entity status. See 37 CFR 1.27

The fee for filing this Appeal Brief is: **$250.00**

☒ A check in the amount of the fee is enclosed.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-0610**. I have enclosed a duplicate copy of this sheet.

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Signature

Dated: **November 9, 2006**

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on **November 9, 2006**.

(Date)

Tammi L. Taylor

Signature of Person Mailing Correspondence

Tammi L. Taylor

Typed or Printed Name of Person Mailing Correspondence

CC:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 09/082,112 Confirmation No. 2322

Applicants : Alberto L. Mendoza

Title : METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER ANIMALS

Filed : May 20, 1998

TC/A.U. : 1645

Examiner : Gangle, Brian J.

Docket No. : MSU 4.1-406

Customer No. : 21036

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF UNDER 37 C.F.R. § 41.37

Sir:

This is an appeal from a final rejection in the above entitled application. The claims on appeal are set forth as Claims Appendix. An oral hearing will be requested. Enclosed is the fee due upon filing of the Brief.

(1) Real Party in Interest

The real party in interest is the Board of Trustees operating Michigan State University, East Lansing, Michigan, a constitutional corporation of the State of Michigan, which is the assignee of the above entitled application.

(2) Related Appeals and Interferences

The present application is a divisional of Application No. 08/895,940 filed July 17, 1997 (now U.S. Patent No. 5,948,413). Application No. 09/998,822, filed November 01, 2001, (now U.S. Patent No. 6,833,136) is a continuation-in-part of Application No. 09/082,232, filed May 20, 1998 (now U.S. Patent No. 6,287,573) which is also a division of Application No. 08/895,940.

A decision by the Board in Appeal No. 2003-1819 for the present Application No. 09/082,112 is attached. There are no other related appeals and interferences.

(3) Status of Claims

Claims 1-15 were cancelled in a preliminary amendment, filed May 20, 1998. Claims 25-27 were cancelled during prosecution of the application. Claims 16-24 were rejected in the final Office Action. Claim 16-24 remain pending in the application and are on appeal.

(4) Status of Amendments

No amendments have been filed subsequent to final rejection.

(5) Summary of Claimed Subject Matter

The claimed subject matter in independent Claim 16 is a method for treatment of an infection caused by *Pythium insidiosum* in human patients using the vaccine prepared according to the method of Example 1 (Specification: page 6, line 34 to page 8, line 2). Specifically, the method of Claim 16 is a method for treatment of an infection caused by *Pythium insidiosum* in human patients (Specification: page 5, lines 13-14, and Example 4 on page 9, line 27 to page 15,

line 31) which comprises:

(a) providing a vaccine containing a mixture of (1) mixed intracellular proteins and (2) mixed extracellular proteins of *Pythium insidiosum* in a sterile aqueous solution (Specification: page 6, line 35 to page 7, line 16 and lines 28-35), wherein the mixed intracellular proteins, which consist essentially of the intracellular proteins removed as a supernatant separated from disrupted cells of the *Pythium insidiosum* grown in a culture medium, and the mixed extracellular proteins, which consist essentially of proteins removed from the culture medium for growing the *Pythium insidiosum* (Specification: page 7, lines 3-16) the mixed intracellular proteins and the mixed extracellular proteins have been precipitated together with acetone, separated and then mixed with water and the mixture has been dialyzed to remove low molecular weight components less than 10,000 MW (Specification: page 7, lines 28-35); and

(b) vaccinating human the patient with the vaccine (Specification: Example 4 on page 10, lines 15-20).

The claimed subject matter in independent Claim 18 is a method for treatment of an infection caused by *Pythium insidiosum* in a mammal (Specification: Example 2, page 8, line 3, to page 9, line 19) which comprises:

(a) providing an injectable vaccine derived from growing cells of *Pythium insidiosum* in a culture medium (Specification: page 6, line 35 through page 7, line 16 and lines 28-35) which comprises in a sterile aqueous solution in admixture:

(1) mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium (Specification: page 7, lines 3-16); and

(2) mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum* (Specification: page 7, lines 3-7);

wherein the admixture of intracellular proteins and extracellular proteins has been precipitated with acetone (Specification: page 7, lines 28-31), separated and admixed with water and then has been dialyzed to remove low molecular weight components less than 10,000 MW (Specification: page 7,

lines 28-35) to produce the vaccine; and

(b) vaccinating the mammal with the vaccine (Specification: Example 2, page 8, line 3, to page 9, line 19).

(6) Grounds of Rejection to Be Reviewed on Appeal

(a) The Examiner objected to the amendment filed 10/8/1999 under 35 U.S.C. §132(a) as introducing new matter into the disclosure.

(b) The Examiner rejected Claim 21 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. This was a new matter rejection.

(c) The Examiner rejected Claims 18 and 20-22 under 35 U.S.C. §103(a) as being unpatentable over Mendoza *et al.* (92a) (*Mycopathologia* 119:89-95, 1992) in view of Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992), Mendoza (95) (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog.

(d) The Examiner rejected Claims 16-17 under 35 U.S.C. §103(a) as being unpatentable over Mendoza *et al.* (92a) (*Mycopathologia* 119:89-95, 1992) in view of Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992), Mendoza (95) (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog as applied to Claims 18, 20-22 above, and further in view of Mendoza *et al.* (96) (*J. Mycol. Med.*, 6:151-164, 1996).

(e) The Examiner rejected Claims 19 and 22-24 under 35 U.S.C. §103(a) as being unpatentable over Mendoza *et al.* (92a) (*Mycopathologia* 119:89-95, 1992) in view of Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992), Mendoza (95) (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog as applied to Claims 18, 20-22 above, and further in view of Blanch *et al.* (*Biochemical Engineering*, Marcel Dekker, Inc., 1996).

(7) Argument

Specification Objection

A. The Examiner objected to the amendment filed 10/8/1999 under 35 U.S.C. §132(a) as introducing new matter into the disclosure. The added material which is objected to is as follows: The amendment changes the deposit number of the strain of *Pythium insidiosum* from ATCC strain 58643 to ATCC strain 74446. This material was deemed as new matter lacking specific written description support in the specification as filed. (The Examiner has also made a new matter rejection. According to MPEP 2163.06 II, a rejection of claims is reviewable by the Board of Patent Appeals and Interferences, whereas an objection and requirement to delete new matter is subject to supervisory review by petition under 37 CFR 1.181. If both the claims and specification contain new matter either directly or indirectly, and there has been both a rejection and objection by the examiner, the issue becomes appealable and should not be decided by petition.)

Pythium insidiosum of the present invention is currently available and has been available from the ATCC under accession number 58643 without restriction since

before the date of the present invention. Deposit ATCC 74446 was made by Applicant under the Budapest Treaty and is identical to the strain of deposit ATCC 58643. Note that Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992) identified ATCC 58643 as CBS 574.85 in the paragraph labeled "Strains" on page 2980. The Budapest Treaty deposit ATCC 74446 is also identified CBS 574.85. (See the enclosed ATCC Budapest Treaty Receipt and Viability Statement for ATCC designation 74446.) As was noted by Examiner, the ATCC product catalog also teaches that strain ATCC 74446 is a deposit of strain ATCC 58643. Since the strain of deposit ATCC 74446 under the Budapest Treaty is identical to strain of deposit ATCC 58643, no new matter is added by the amendment. Reversal of the objection is requested.

Claim Rejections- 35 U.S.C. §112

B. The Examiner rejected Claim 21 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims were rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, this was a new matter rejection.

As argued above, deposit ATCC 74446 was made under the Budapest Treaty and is identical to the strain of deposit ATCC 58643. (See the enclosed ATCC Budapest Treaty Receipt and Viability Statement for ATCC designation 74446, mailed on March 21, 2006.) It is therefore not new matter. Reversal of the rejection is requested.

Claim Rejections- 35 U.S.C. §103

C. The Examiner rejected Claims 18 and 20-22 under 35 U.S.C. §103(a) as being unpatentable over Mendoza *et al.* (92a) (*Mycopathologia* 119:89-95, 1992) in view of Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992), Mendoza (95) (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog.

To establish a *prima facie* case of obviousness, three criteria must be met (MPEP §2143). First, there must be some suggestion or motivation to combine the reference teachings. The teaching and the suggestion to make the claimed combination must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Independent of the Applicant's disclosure in this case there is no suggestion or motivation to combine the prior art to produce the vaccine of the claimed method.

Mendoza *et al.* (92a) teaches two vaccines, a soluble concentrated antigen vaccine (SCAV) consisting solely of extracellular antigens that are extruded by the cell into the medium, and a cell-mass vaccine (CMV)

consisting of both the soluble and insoluble intracellular antigens. Both vaccines were of limited value for treating horses infected greater than 0.5 months but less than 2 months, and neither vaccine was effective for treating horse that had been infected for more than 2 months. (Mendoza *et al.* (92a): page 92, Table 1) Mendoza *et al.* (92a) teaches that the CMV has several drawbacks because it has a short shelf-life and it causes severe inflammatory reactions at the vaccination site. (Mendoza *et al.* (92a): Abstract, page 89).

Mendoza *et al.* (92b) teaches the preparation of a mixture of intracellular proteins from *Pythiosis insidiosum* for use in Western blots. Mendoza *et al.* (92b) teaches using the preparation of soluble intracellular proteins for SDS-polyacrylamide gel electrophoresis to identify immunodominant proteins in the preparation such as the 28, 30, and 32 kD proteins. Mendoza *et al.* (92b) teaches that the cells were disrupted and then the disrupted cell debris removed by centrifugation to produce a supernatant containing soluble intracellular proteins. A person of ordinary skill in the art will recognize that the reason that the disrupted cell debris was removed from the

intracellular proteins was to prevent the disrupted cell debris from clogging up the gel well which would prevent the intracellular antigens from entering the gel properly. Mendoza *et al.* (92b) suggests that the 28, 30, and 32 kD proteins that were identified may be useful for diagnostic purposes and as candidates for vaccination trials, but does not actually disclose a vaccine. Mendoza (95) teaches that the discovery of the fact that at least three prominent proteins (28-32 kD) were present by Western blot analysis of sera from equine cases, opened the possibility to use those antigens for immunotherapy. Sixteen horses with chronic Pythiosis were vaccinated with a mixture of the culture filtrated proteins and the 28-32 kD immunodominant proteins. Eight of the vaccinated horses were cured.

In the claimed methods, the provided vaccine has the low molecular weight components less than 10,000 MW removed. Thus, the larger molecular weight components remain in the vaccine. Amicon 1993 catalog teaches the PM10 membrane will retain molecules larger than 10,000 MW, and the Fisher 1995 catalog teaches dialysis membrances which retain molecules larger than 10,000 MW. Mendoza *et al.* (92b) teaches that the soluble intracellular preparations of

P. insidiosum have many proteins bands larger than 10,000 MW as illustrated by Coomassie brilliant blue staining in Figure 1 ranging from 97,000 to 14,000 in molecular weight. At least 33 to 38 bands were detected in each strain. Most bands in the Coomassie blue stained gel were located at high molecular weights (97,000 to 28,000) in the five *P. insidiosum* strains. Bands ranging from 100,000 to 14,000 and lower in molecular weight were detected in silver-stained gels (Mendoza *et al.* (92b): Page 2981, Figure 1B). An increase in the number of bands in all *P. insidiosum* strains, especially in the lower-molecular-weight range (28,000 and lower) was observed with these gels. The five serum samples from horses with proven pythiosis recognized at least 20 antigens observed in the SDS-PAGE gels (Mendoza *et al.* (92b): Page 2981, Figure 2). While, the 32k, 30k and 28k bands were particularly prominent, most of the antigens detected by these sera ranged in molecular weight from 68,000 to 14,000. Therefore, it is clear that the soluble mixture of intracellular proteins includes many proteins, including many other antigens besides the three 32k, 30k and 28k prominent antigens that horses will react against.

As far as one skilled in the art would know

considering Mendoza *et al.* (92a), the soluble intracellular protein composition of Mendoza *et al.* (92b), would still have a short shelf-life. In addition, since it includes numerous intracellular protein antigens as found in the cell-mass vaccine (CMV) of Mendoza *et al.* (92a), one skilled in the art would conclude that a horse would produce a prominent inflammatory response at the site of inoculation with the vaccine, as taught by Mendoza *et al.* (92a). Since these are undesirable properties in a vaccine, one of ordinary skill in the art, in view of Mendoza *et al.* (92a) and Mendoza *et al.* (92b), would not be motivated to create a vaccine containing all of the soluble intracellular proteins greater than 10,000 MW for treating Pythiosis in mammals. A person of ordinary skill in the art would not be motivated to add any additional proteins beyond the three prominent proteins (28-32 kD) of the vaccine of Mendoza (95) to avoid the prominent inflammatory response described by Mendoza *et al.* (92a).

Basic considerations set out in MPEP §2141 which apply to obviousness rejections include a requirement that the claimed invention must be considered as a whole, and that the references must be viewed without the benefit of

hindsight reasoning. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). According to M.P.E.P. §716.02(a), the presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *Ex parte Thumm*, 132 USPQ 66 (Bd. App. 1961). More specifically, the absence of property which a claimed invention *would have been expected to possess based on the teachings of the prior art* is evidence of unobviousness. *Ex parte Mead Johnson & Co.* 227 USPQ 78 (Bd. Pat. App. & Inter. 1985) (Based on prior art disclosures, claimed compounds would have been expected to possess beta-adrenergic blocking activity; the fact that claimed compounds did not possess such activity was an unexpected result sufficient to establish unobviousness within the meaning of 35 U.S.C. 103). Applicants claim a method providing a vaccine having the enhanced curative properties of the vaccine of Mendoza (95) that are lacking in the SCAV and CMV vaccines of Mendoza *et al.* (92a), while not having the undesirable property of causing inflammation as seen with the CMV vaccine described by Mendoza *et al.* (92a). Of the seven horses injected with the vaccine of the claimed method that

had chronic pythiosis, four were cured. While all of the cured horses developed an inflammatory reaction at their vaccination sites, the reactions were mild (Specification: page 8, lines 27-28). When the vaccine was used to vaccinate a 14 year old boy infected with *Pythium insidiosum*, a wheal and flare reaction developed at the reaction site, with no other side effects except for itching of the injection site (Specification: page 10, lines 22-26; and page 15, lines 17-20). The mild inflammatory reactions are unexpected results, considering the prior art teachings of Mendoza *et al.* (92a). Mendoza *et al.* (92a) found that the CMV vaccine caused a prominent inflammatory response at the site of inoculation. "Half of the horses vaccinated with CMV developed violent reactions with sterile abscesses." (Mendoza *et al.* (92a): page 91, first column, "*Results*"). While it is true that Mendoza *et al.* (92a) teaches that the reaction was apparently a function of the amount of vaccine inoculated, a person of skill in the art would not be motivated to *decrease* the amount of vaccine inoculated when Mendoza *et al.* (92a) teaches that the CMV is not even effective for treatment of chronic cases at the concentrations described in Mendoza *et al.* (92a). (Mendoza

et al. (92a): Table 1).

In the claimed methods, the vaccine has the low molecular weight components less than 10,000 MW removed. The larger molecular weight components (greater than 10,000 MW) remain in the vaccine. A person of ordinary skill in the art, reading the cited references, would not be motivated to provide the vaccine of the claimed methods. The cited references suggest to a person of skill in the art that the vaccine provided in the claimed methods would have undesirable properties. The references teach away from a vaccine having all of the larger molecular weight components present in the vaccine because of these expected properties. Likewise, it would be unexpected that such a vaccine would not cause severe inflammation and sterile abscesses at the injection site considering the teachings of the cited references. While Mendoza (95) teaches that adding the three prominent proteins (28-32 kD) improved the earlier vaccine of Mendoza *et al.* (92a) consisting solely of extracellular antigens, it does not show or suggest that the vaccine of the claimed method could also cure chronic pythiosis without causing the inflammation problem associated with the CMV of Mendoza *et al.* (92a). Reversal

of the rejection is requested.

D. The Examiner rejected Claims 16-17 under 35 U.S.C. §103(a) as being unpatentable over Mendoza *et al.* (92a) (*Mycopathologia* 119:89-95, 1992) in view of Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992), Mendoza (95) (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog as applied to Claims 18, 20-22 above, and further in view of Mendoza *et al.* (96) (*J. Mycol. Med.*, 6:151-164, 1996).

Mendoza *et al.* (96) teach human pythiosis and the need for an effective treatment for humans. Mendoza *et al.* (96) also teach the benefits of vaccination of horses with the Miller and Mendoza vaccines. However, for the reasons discussed above, taken alone or in combination with the other cited references, Mendoza *et al.* (96) does not show or suggest to a person of ordinary skill in the art that a vaccine with soluble intracellular proteins as prepared in the claimed method would not have an inflammation problem associated with the CMS vaccine. Thus, it would not be obvious to a person of ordinary skill in the art that such a vaccine would be safe enough for treating of humans.

Mendoza *et al.* (92a) found that the CMV vaccine caused a prominent inflammatory response and violent reactions with sterile abscesses developed in half of the horses vaccinated. Therefore, nothing in Mendoza *et al.* (96), taken alone or in combination with the other cited references, would motivate a person of skill in the art to provide a vaccine as in the claimed methods to treat human patients. In addition to the treatment of the Thai boy discussed above, as seen in paragraph 8 of the Declaration under 37 CFR 1.132, mailed on March 21, 2006, the vaccine of the present invention has been shown to be a good choice to treat human pythiosis when all the surgical and chemotherapeutic options have failed. Nothing in the cited prior art references would suggest that human treatment would be possible. The references must be viewed without the benefit of impermissible hindsight vision. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). Reversal of the rejection is requested.

E. The Examiner rejected Claims 19 and 22-24 under 35 U.S.C. §103(a) as being unpatentable over Mendoza *et al.* (92a) (*Mycopathologia* 119:89-95, 1992) in view of Mendoza *et al.* (92b) (*J. Clinical Microbiol.*, 30:2980-2983, 1992), Mendoza (95) (3rd NIAID Workshop in Med. Mycol. Series Abstracts, 1995), Amicon 1993 catalog, and Fisher 1995 catalog as applied to Claims 18, 20-22 above, and further in view of Blanch *et al.* (*Biochemical Engineering*, Marcel Dekker, Inc., 1996).

Blanch *et al.* teach that "protein precipitation is usually an intermediate step toward final purification, since precipitates are typically impure. They may be aggregates of several proteins..." (Blanch *et al.*: page 491, second paragraph). Blanch *et al.* teach that one of the methods of precipitating proteins is through the addition of acetone. When using acetone, Blanch *et al.* show that the precipitation is related to the solute molecular weight. (Blanch *et al.*: equation, second paragraph of page 496) Blanch *et al.* therefore makes it clear that several proteins would be precipitated when using acetone.

Blanch *et al.*, either taken alone or in combination with the other cited references, does not show

or suggest a vaccine having the enhanced curative properties of the vaccine of Mendoza (95) that are lacking in the SCAV and CMV vaccines of Mendoza *et al.* (92a), while not having the property of causing inflammation as seen with the CMV vaccine described by Mendoza *et al.* (92a). Therefore, nothing in Blanch *et al.*, taken alone or in combination with the other cited references, would motivate a person of skill in the art to provide a vaccine as in the claimed methods. Reversal of the rejection is requested.

F. Conclusion

In light of the above, Claims 16-24 are patentable and in condition suitable for allowance. Attached is the ATCC Budapest Treaty Receipt and Viability Statement for ATCC designation 74446. A copy of a Declaration under 37 CFR 1.132, mailed on March 21, 2006, (originally filed for Application Serial no. 09/082,232, filed July 17, 1997, now U.S. Patent No. 6,287,573) is attached. The Declaration shows the minor side effects caused in equines (paragraph 5) and humans (paragraph 8) when using the vaccine. Reversal of the Final Rejection is requested.

Respectfully,

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CLAIMS APPENDIX

16. A method for treatment of an infection caused by *Pythium insidiosum* in human patients which comprises:

(a) providing a vaccine containing a mixture of (1) mixed intracellular proteins and (2) mixed extracellular proteins of *Pythium insidiosum* in a sterile aqueous solution, wherein the mixed intracellular proteins, which consist essentially of the intracellular proteins removed as a supernatant separated from disrupted cells of the *Pythium insidiosum* grown in a culture medium, and the mixed extracellular proteins, which consist essentially of proteins removed from the culture medium for growing the *Pythium insidiosum* the mixed intracellular proteins and the mixed extracellular proteins have been precipitated together with acetone, separated and then mixed with water and the mixture has been dialyzed to remove low molecular weight components less than 10,000 MW; and

(b) vaccinating human the patient with the vaccine.

17. The method of Claim 16 wherein vaccinating the patient with the vaccine is subcutaneous.

18. A method for treatment of an infection caused by *Pythium insidiosum* in a mammal which comprises:

(a) providing an injectable vaccine derived from growing cells of *Pythium insidiosum* in a culture medium which comprises in a sterile aqueous solution in admixture:

(1) mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium; and

(2) mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum;*

wherein the admixture of intracellular proteins and extracellular proteins has been precipitated with acetone, separated and admixed with water and then has been dialyzed to remove low molecular weight components less than 10,000 MW to produce the vaccine; and

(b) vaccinating the mammal with the vaccine.

19. The method of Claim 18 wherein the removed proteins in the admixture have been provided by growing cells of the *Pythium insidiosum* in the culture medium, then killing the cells, then separating the killed cells from the culture medium to produce a first supernatant to provide the mixed extracellular proteins of (a)(2) and then disrupting the killed cells in sterile water and removing the disrupted cells from the sterile water containing the mixed intracellular proteins to provide the mixed intracellular proteins of (a)(1) in a second supernatant, combining the first and second supernatants, precipitating the proteins with the acetone, resuspending the precipitated proteins in sterile water, and dialyzing the resuspended proteins in sterile water to remove the material less than 10,000 MW.

20. The method of Claim 18 wherein the cells have been disrupted by sonication.

21. The method of Claim 18 wherein the *Pythium insidiosum* is deposited as ATCC 74446.

22. The method of any one of Claims 19, 20 or 21 wherein the culture medium is Sabouraud's dextrose broth.

23. The method of Claim 19 wherein the cells are killed with thimersol.

24. The method of Claim 19 wherein the disrupted cells are removed from the sterile water containing the mixed intracellular proteins by centrifugation to provide the mixed intracellular proteins of (a)(1) in the second supernatant.

EVIDENCE APPENDIX

Attached are copies of the following evidence:

1. ATCC Budapest Treaty Receipt and Viability Statement for ATCC designation 74446, mailed on March 21, 2006.

2. Declaration under 37 CFR 1.132, mailed on March 21, 2006 and considered by the Examiner in the final Office Action mailed June 14, 2006. (The Declaration was originally filed in U.S. Patent Application No. 09/082,232, now U.S. Patent No. 6,287,573).

RELATED PROCEEDINGS APPENDIX

Attached are copies of the following decisions on appeal:

1. Decision by the Board in Appeal No. 2003-1819 for the present U.S. Patent Application No. 09/082,112.

ATCC

10801 University Blvd Manassas, VA 20110-2209 Telephone: 703-365-2700 FAX: 703-2745

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Michigan State University, Medical Technology Program
Attn: Alberto Leonel Mendoza
322 N. Kedzie Lab
East Lansing, MI 48824-1031

Deposited on Behalf of: **Michigan State University**

Identification Reference by Depositor:	**ATCC Designation**
Pythium insidiosum CBS 574.85 (originally labelled H-9)	74446

The deposit was accompanied by: a scientific description __X__ a proposed taxonomic description indicated above.
The deposit was received June 1, 1998 by this International Depository Authority and has been accepted.

AT YOUR REQUEST:

~~X~~ We will not inform you of requests for the strain.
X The strain is available to the scientific public upon request as of June 1, 1998.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested July 15, 1998. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA

Signature of person having authority to represent ATCC:
Barbara M. Hailey
Barbara M. Hailey, Administrator, Patent Depository

Date: July 20, 1998

cc: **Ian C. McLeod (Ref. Docket MSU 4.1-356)**

MSU 4.1-405
7/27/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Alberto L. Mendoza

Serial No.: 09/082,232 Group Art Unit 1645

Filed : 1998 May 20

For : METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER ANIMALS

Examiner : N. Minnifield

Assistant Commissioner for Patents

Washington, D. C. 20231

DECLARATION UNDER 37 CFR 1.132

Dear Sir:

The inventor, Alberto L. Mendoza, states as follows:

(1) Results were obtained in 30 new vaccinated equines with granulomatous lesions on different parts of their bodies and two humans from Thailand with infections caused by *P. insidiosum*. The diagnosis of pythiosis was confirmed in all equines and the two humans by serology. An immunodiffusion test and an ELISA specific to *P. insidiosum* infections were used (Mendoza, L., et al., Clin. Diagnost. Lab. Immuno. 4:715-718 (1997); and Mendoza, L., et al., J. Clin. Microbiol. 13: 813-816 (1986)). In some cases the diagnosis of equine pythiosis were also confirmed by

histopathology and in a few instances by culture. In the two human cases histopathology, culture, and cytokines profile were performed.

(2) Data was obtained before and post vaccination from 20 horses. In the remaining 10 horses no data, during the vaccination trial, were available (the owners and/or veterinarian practitioners did not report the data). In these ten cases, I was informed that eight of the ten horses were cured, while two did not respond to vaccination.

(3) This study was conducted in coordination with Bio-Medical International, Austin, Texas. This company possesses a USDA permit for the experimental use of the PIV in horses. The study in the 20 horses was conducted from 1997 to 1999. The equines in this study were located in different areas of southern Texas. The vaccinated equines were of different breeding backgrounds. Their ages were between 8 months and 20 years old and the chronicity of the lesions was one month or less. In four cases, however, the lesions were observed for more than two months.

(4) All cases of equine pythiosis in the study of paragraph (3) were vaccinated in the middle of the horses's neck with 100 μl of the *Pythium insidiosum* vaccine (PIV) (2.0 mg/ml) as described in Examples 1 and 2 and as claimed in the above referenced application. The PIV was applied twice. The second vaccine always took place fourteen days after the first

dose. The rationale for the second vaccination were based on the fact that the PIV does not trigger a protective immune response but a curative immunity of short duration. Research has shown that the response after vaccination is linked to T-helper cells (Th1) subset which triggers a cellular immunity, mainly T cytotoxic lymphocytes (Dixon, D. M., et al., Med. Mycol. 36 (Suppl. 1): 57-67 (1998); and Thitithanyanont, A., et al., Clin. Infec. Dis. 27:1394-1400 (1998)).

(5) In 20 vaccinated equines of paragraph (3) (horses with collected data) a mild delay type hypersensitivity (DTH) was observed at the site of vaccination (around 8 to 20 mm in diameter). Itching and the DTH response at the site of vaccination were the only two observed side effects. The DTH reaction disappeared seven days after vaccination. No other side effects were observed. Eighteen (18) equines cases were cured after vaccination. Two (2) chronic cases responded at first and then lesions reappeared. After this, vaccination did not work any more.

(6) The overall rate of cure in this new trial in horses was 87%, including the horses of paragraphs (2) and (3).

(7) In 1992, Mendoza et al (Mendoza, L., et al., Mycopathologia 119:89-95 (1992)) found that horses with pythiosis responded to the vaccine described therein according to the duration of their lesions. In

that study all acute cases (100%) were cured by the vaccine described therein, while none of the chronic cases (2 months or more) responded to vaccination. In that study, most equine cases had pythiosis for a month or less (acute cases). With the PIV of the present invention fifty percent (50%) of the chronic cases were cured. This property was absent in the earlier vaccines of the prior art.

(8) In addition to the Thai boy cured by the PIV described in the application, two new cases were treated in Thailand. One of them is currently being treated, the other responded very well to the PIV. These new trials in humans suggest that the vaccine is a good choice to treat human pythiosis when all the surgical and chemotherapeutic options have failed. The PIV generated minor side effects at the vaccination site (itching and a DTH response) in both humans and equines. This new trial confirmed previous reports of the minor side effects and safety of the PIV in humans and animals.

(9) In previous studies in equines and three humans from Thailand with the disease, the appearance of a DTH response at the site of vaccination was indicative of cure in the vaccinated humans and animals (Dixon, D. M., et al., Med. Mycol. 36 (Suppl. 1): 57-67 (1998); Mendoza, L., et al., Mycopathologia 119:89-95 (1992); and Thitithanyanont, A., et al., Clin. Infec. Dis. 27:1394-1400 (1998). This study confirmed those

reports.

(10) The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Albert L. Mendoza
Date: 07/28/99

Paper No. 45

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ALBERTO L. MENDOZA

Appeal No. 2003-1819
Application No. 09/082,112

ON BRIEF

Before SCHEINER, MILLS, and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 16-25, which are the claims on appeal in this application.

Claims 16, 18 and 19 are illustrative of the claims on appeal and appear below.

16. A method for treatment of Pythiosis in human patients having the Pythiosis which comprises:

(a) providing a vaccine containing a mixture of mixed intracellular proteins and mixed extracellular proteins of *Pythium insidiosum* in a sterile aqueous solution, wherein the mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* grown in a culture medium, and the mixed extracellular proteins, which consist essentially of proteins removed from the culture medium for growing *Pythium insidiosum*, are in water and the mixture has been dialysed to remove molecular weight components less than 10,000 MW; and

(b) vaccinating the patient with the vaccine.

Docketed
March 28, 2005

cc: A. Mendoza
J. Sherman
2/1/05

18. A method for the treatment of Pythiosis in a mammal having the Pythiosis which comprises:

(a) providing an injectable vaccine derived from growing cells of *Pythium insidiosum* in a culture medium which comprises in a sterile aqueous solution in admixture:

(1) mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium; and

(2) mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*;

wherein the admixture in water has been dialyzed to removed low molecular weight components less than 10,000 MW to produce the vaccine; and

(b) vaccinating the mammal with the vaccine.

19. The method of claim 18 wherein the removed proteins in the admixture have been provided by growing cells of the *Pythium insidiosum* in the culture medium, then killing the cells, then separating the killed cells from the culture medium to produce a first supernatant to provided the mixed extracellular proteins of (a)(2) and then disrupting the killed cells in sterile water and removing the disrupted cells from the sterile water containing the mixed intracellular proteins to provide the mixed intracellular proteins of (a)(1) in a second supernatant, combining the first and second supernatants, precipitating the proteins, resuspending the precipitated proteins in sterile water, and dialyzing the resuspended proteins in sterile water to remove the material less than 10,000 MW.

The prior art references cited by the examiner[1] are:

Mendoza et al (Mendoza 1996), J. Mycol. Med. Vol. 6, pp. 151-164 (1996)

Mendoza et al. (Mendoza 1992a), Mycopathologica, Vol. 119, pp. 89-93 (1992)

Mendoza et al. (Mendoza 1992b), J. Clin. Microbiol., pp. 2980-2983 (1992)

Mendoza et al. (Mendoza 1995), Third NIAID Workshop in Medical Mycological Series (Abstract), Sept. 7-9 (1995)

Sigma Catalog, p. 1874 (1992)

Amicon Catalog, p. 35 (1993)

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[1] For ease of reference to the Answer, we adopt the Examiner's reference naming scheme.

Grounds of Rejection

Claims 19 and 24 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite.

Claims 16-25 stand rejected under 35 U.S.C. §103, as obvious over Mendoza 1996, Mendoza 1992a, Mendoza 1992b, Mendoza 1995, Sigma Catalog and Amicon Catalog.

We reverse the rejection of claims 19 and 24 under 35 U.S.C. §112, second paragraph, as indefinite. We affirm the rejection of claims 16-25 under 35 U.S.C. §103, as obvious over Mendoza 1996, Mendoza 1992a, Mendoza 1992b, Mendoza 1995, Sigma Catalog and Amicon Catalog.

Claim Grouping

According to appellant, 16 and 17 stand or fall together for the rejection under 35 U.S.C. §103. Brief, page 7. Claims 19 and 24 are grouped together with respect to the rejection under 35 U.S.C. §112, second paragraph. We select claims 16 and 19 as representative of each rejection, respectively. 37 CFR 1.192(c)(7) (2003).

DISCUSSION

35 U.S.C. §112

Claims 19 and 24 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite.

It is the examiner's position that the phrase, "removing the disrupted cells to provide the mixed intracellular proteins" in claims 19 and 24, is indefinite. Answer, page 3. The examiner argues that one of ordinary skill in the art would not know what is being removed or what steps are being performed. The examiner surmises that, "Appellants appear to be referring to the removal of insoluble cellular material via centrifugation and removal of the supernatant with discarding of the pellet. Yet the artisan does not readily recognize how removal of disrupted cells may be achieved and therefore the recited step is indefinite as to what step is being performed and its subsequent effect on the vaccine prepared by the recited method." Answer, pages 3-4.

Appellant responds, arguing that, "the most common method for removing the disrupted killed cells is centrifugation and that after centrifugation, the supernatant fraction would contain the mixed intracellular proteins. Furthermore, to provide guidance to one of ordinary skill in the art, the applicant teaches in Example 1 disrupting the killed cells in sterile water by sonication and then removing the killed cells by centrifugation." Brief, page 8. According to the Answer, the examiner also appears to have reasonably understood the claim as referring to a centrifugation method and the product resulting from performance of a centrifugation method. Thus, we agree with appellant, that when the claims are read in view of the specification, one of ordinary skill in the art at the time of the invention would have been able to discern the claim scope.

In view of the above, we reverse the rejection of claims 19 and 24 under 35 U.S.C. §112, second paragraph.

35 U.S.C. §103

Claims 16-25 stand rejected under 35 U.S.C. §103, as obvious over Mendoza 1996, Mendoza 1992a, Mendoza 1992b, Mendoza 1995, Sigma Catalog and Amicon Catalog.

According to the examiner, Mendoza 1992a discloses two prior art Pythium insidiosum vaccines, a cell-mass vaccine (CMV)[2] and a soluble concentrated antigen vaccine (SCAV).[3] Answer, page 4.

The examiner acknowledges that neither of the CMV or SCAV vaccines of Mendoza et al., 1992a are the vaccines as disclosed in Example 1 of the specification, as "neither of the prior art vaccines has isolated cytoplasmic antigens added to the preparations." Paper No. 32, page 4. The examiner, however, acknowledges that specification, Example 1 references that the prominent cytoplasmic antigens added to Mendoza's original vaccine[4] (SCAV vaccine) were as described in Mendoza 1992b. Id.

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[2] Appellant characterizes the CMV of the prior art as an intracellular protein vaccine. Brief, page 10. Appellant characterizes the SCAV vaccine of the prior art as an extracellular protein vaccine. Id.

[3] Based on the guidance in Example 1 of the specification, the examiner understands that for the claimed vaccine, isolated antigens were added to the vaccine of Mendoza's earlier publication in 1986 which corresponds to the SCAV vaccine. Paper No. 32, page 4.

[4] Mendoza's original vaccine is defined in the specification as composed of culture filtrated antigens, and is later referenced in Mendoza 1992b. Specification, page 3.

Significantly, in support of the rejection the examiner relies on Mendoza 1995 which teaches the addition of the 28-32 kD (intracellular) immunodominant peptides (from CMV) to culture filtrate proteins (SCAV) leads to the cure of 8 infected horses. Answer, page 4. Thus, it would reasonably appear that Mendoza 1995 describes that specific, prominent cytoplasmic intracellular antigens of Mendoza 1992b were added to the SCAV vaccine (mixed extracellular preparation). Answer, page 4. The addition of these intracellular cytoplasmic antigens described in Mendoza 1992b to the SCAV as described in Mendoza 1995 provides for an improved vaccine which cures chronically infected horses. Answer, page 4.

The examiner understands that the vaccine of Mendoza 1995 is "different from the vaccine claimed in that the claimed vaccine is essentially a combination, a vaccine which combines the elements of the CMV and SCAV preparations (mixed intracellular and mixed extracellular proteins) of the prior art" whereas the vaccine of Mendoza 1995 is a mixture of specific isolated antigens from the CMV added to the SCAV. Paper No. 32, page 5. Mendoza 1996 is relied on by the examiner for its indication of the similarity in human and animal Pythiosis infections, and that the same immunodominant antigens were recognized in both horse and human sera. Answer, page 7. From this evidence, the examiner submits that one of ordinary skill in the art would expect beneficial results of the vaccine in humans.

The examiner finds that the (Answer, page 5)

> suggestion of the prior art is that the combination of mixed intracellular and extracellular proteins provide the enhanced curative properties to chronically infected horses. In addition, upon such teaching, the combination of the CMV (containing the immunodominant proteins) and the SCAV (mixed extracellular) proteins would have been prima facie obvious to the artisan, particularly in that the combination of the two preparations would provide the required constituents yet would be easier in preparation than providing only the isolated immunodominant proteins because there would be no need for the additional preparative steps including isolation of the 28-32 kD antigens via gel electrophoresis recovery from the gel and addition to the SCAV vaccine.

We agree that the examiner has established a prima facie case of obviousness. In our view the mixed intracellular proteins of the claimed vaccine read on the mixture of 28-32 kD immunodominant proteins of Pythium insidiosum described in the prior art vaccine of Mendoza 1995.[5]

Where the prior art, as here, provides a reason suggestion or motivation to make the claimed invention, the burden then falls on an appellant to rebut that prima facie case. Such rebuttal or argument can consist of any other argument or presentation of evidence that is pertinent. In re Dillon, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991).

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[5] In an alternative, acceptable theory of the prima facie case, the examiner suggests that one of ordinary skill in the art would have been motivated to substitute the CMV of Mendoza 1992b for the 28-32 kD immunodominant proteins of the vaccine of Mendoza 1995 with an expectation of success because the immunodominant proteins of Mendoza 1995 "are present in the CMV preparation." Answer, page 11

Appellant would appear to acknowledge that the CMV vaccine of the prior art is an intracellular protein vaccine, and the SCAV vaccine is an extracellular protein vaccine. Brief, page 10. Appellant also acknowledges that Mendoza 1995 discloses "an SCAV vaccine containing three immunodominant intracellular proteins." Brief, page 12. Appellant argues that even so, the prior art does not suggest to a person of ordinary skill in the art to make a vaccine that contain all the soluble intracellular proteins (but not the insoluble proteins) and the extracellular proteins. At best, one of ordinary skill in the art would most likely be motivated to make a vaccine consisting of the SCAV and the three immunodominant proteins." Brief, page 13.

The examiner responds, arguing that the presence of, "[a]ll of the intracellular proteins are not required by the claims." Answer, page 12. The examiner further argues that, "the elements of the claimed invention, i.e., mixed intracellular and mixed extracellular proteins are provided and are within the scope of the claim regardless of whether all of the intracellular antigens or merely the immunodominant intracellular antigens are provided." Id. We agree with the examiner's claim interpretation, and find that the claims before us do not require all of the intracellular proteins of the CMV, only a mixture of these proteins. Nor do the claims specifically require only soluble intracellular proteins with the exclusion of all insoluble proteins, as argued by appellant.

Appellant argues that there is nothing in the Mendoza references cited which would suggest to one of ordinary skill in the art that adding only the soluble intracellular proteins of the CMV to the SCAV would produce a vaccine with an efficiency superior to

either prior art vaccine and which would not have the undesirable attributes of CMV. Brief, page 14. However, we agree with the examiner that the claims are not limited to only the soluble intracellular proteins of the CMV. The claims recite "(1) mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the Pythium insidiosum separated from the culture medium." There is no indication in the specification or otherwise, that the mixed intracellular protein of the specification does not contain any soluble protein material, or that the inclusion of insoluble protein material would affect the basic and novel characteristics of the claimed subject matter.[6]

The examiner further submits that there is no comparative data of record which demonstrates different or unexpected effects which are attributed to a preparation containing all the intracellular proteins in comparison to one containing only the immunodominant peptides. Answer, page 12. To this end we acknowledge that Mendoza 1995 describes the enhancement of the therapeutic effect of the SCAV vaccine by adding the hyphal proteins of Pythium insidiosum. See Title, p. 9. It would reasonably appear that an enhanced or superior result would have been expected from a vaccine comprising the immunodominant proteins of the CMV described in Mendoza 1995 and additional intracellular proteins of the CMV. Expected beneficial results are evidence of obviousness just as unexpected beneficial results are evidence of

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[6] The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976).

unobviousness. See In re Skoner, 517 F.2d 947, 950, 186 USPQ 80, 82 (CCPA 1975).

Next, Appellant argues that "unlike the applicant's vaccine, both vaccines made in view of the prior art would contain material less than 10,000 MW." Id. According to appellant, the composition of Mendoza 1992a, containing soluble intracellular proteins, further includes material less than 10,000 MW and insoluble proteins. Brief, page 14.

The examiner responds, arguing, "the method/process limitations of filtration via ultracentrifugation or a stir cell through a PM-10 membrane remove small peptides and impurities as ... evidenced by ... Amicon catalog p. 35. Again a stir cell removes small constituents with a molecular weight less that [sic] 10,000MW. The small constituents flow through the membrane with the wash fluid. This step is an obvious equivalent which does not appear to result in a patentably distinguishable product from that of dialysis to remove small peptides and impurities because the molecular weight cut offs for the PN-10 membrane and a dialysis membrane are similar as evidenced by Sigma, Amicon and Mendoza et al., 1992(b). Sigma teaches dialysis tubing with a molecular weight cutoff of approximately 12,400 MW and PM-10 membrane of MW cut-off of 10,000 MW."

In our view, Appellant has failed to sufficiently respond to the examiner's evidence that claimed dialysis MW cut offs and the prior art filtration cutoffs are equivalent. Answer, page 13. Appellant continues to argue that the claimed method "steps and the order they are performed produces a vaccine which is not equivalent to a mixture of either the CMV and the SCAV or the intracellular protein preparation in

Mendoza (1992b) and the SCAV", but fails to explicitly explain a difference in the two. Reply Brief, page 8.

This argument of appellant is mere attorney argument which is unsupported by evidence. Appellant is reminded that arguments of counsel cannot take the place of evidence. In re DeBlauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), In re Payne, 606 F.2d 303, 315, 203 USPQ 245, 256 (CCPA 1979). In addition, appellant's Example 1, specification, page 6, admits that "the improved vaccine was prepared by adding cytoplasmic antigens to the earlier *P. insidiosum-vaccine* (Mendoza et al., Mycopathological 119:89-95 (1992)." Appellant has presented no evidence indicating a difference in the earlier *P. insidiosum-vaccine* of the prior art, Mendoza 1992a, and the mixed extracellular product claimed.

In view of the above, we do not find appellant has put forth sufficient argument or evidence to rebut the examiner's prima facie case of obviousness. The rejection of the claims for obviousness is affirmed.

CONCLUSION

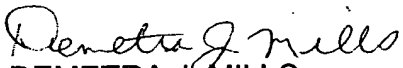
The rejection of claims 19 and 24 under 35 U.S.C. §112, second paragraph, as indefinite is reversed.

The rejection of claims 16-25 under 35 U.S.C. §103, as obvious over Mendoza 1996, Mendoza 1992a, Mendoza 1992b, Mendoza 1995, Sigma Catalog and Amicon Catalog is affirmed.

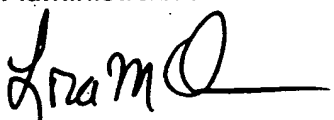
No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

TONI R. SCHEINER
Administrative Patent Judge



DEMETRA J. MILLS
Administrative Patent Judge



LORA M. GREEN
Administrative Patent Judge

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Appeal No. 2003-1819
Application No. 09/082,112

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